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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Dominique Lesuisse, et al

Application No.: **10/613,899**

Filed: **September 28, 2004**

Title: **Derives Tetracycliques Amino Indazoles, Procede De Preparation Et Intermediaires De Ce Procede a Titre De Medicaments Et Compositions Pharmaceutiques Les Renfermant**

Examiner: Not Yet Assigned

Group Art Unit.: Not Yet Assigned

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Applicants submit herewith an English translation of the above-mentioned U.S. Provisional Application. Also submitted herewith is a statement by the translator of the accuracy of the translation.

This submission and request for entry is being made to satisfy the requirements under 37 C.F.R. 1.78(a)(5).

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Respectfully submitted,

October 11, 2005

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UNITED STATES PATENT AND TRADEMARK OFFICE

I, Susan ANTHONY BA, ACIS,

Director of RWS Group Ltd, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That the translator responsible for the attached translation is well acquainted with the French and English languages.

3. That the attached is, to the best of RWS Group Ltd knowledge and belief, a true translation into the English language of the specification in French filed with the application for a patent in the U.S.A. on September 28, 2004
under the number 60/613,899

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.

For and on behalf of RWS Group Ltd

The 29th day of September 2004

FRAV2004/0020

FRANCE

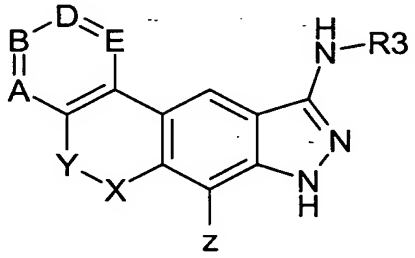
PATENT

TETRACYCLIC AMINOINDAZOLE DERIVATIVES, PREPARATION PROCESS AND INTERMEDIATES OF THIS PROCESS AS MEDICINAL PRODUCTS, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.

AVENTIS PHARMA SA.

ABSTRACT

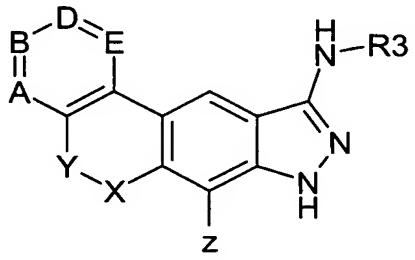
The present invention relates to the novel derivatives of formula (I)



in which R3 represents a hydrogen or a group –C(O)-R4; A, B, D and E represent, independently of one another, a CH or an N, in the knowledge that there are at most two nitrogens; X represents a radical O, S, NR, CH_2, $(CH_2)_2$ or $(CH_2)_3$; Y represents a radical CH_2, $(CH_2)_2$, CO, CS, (C=NH), O, S, NR, $C=CH_2$ or C-CHRa; Z is a hydrogen or a halogen; to the isomers thereof, the mixtures thereof, the racemic mixtures, enantiomers, diastereoisomers and tautomers thereof, and also the pharmaceutically acceptable salts thereof.

TETRACYCLIC AMINOINDAZOLE DERIVATIVES, PREPARATION PROCESS AND INTERMEDIATES OF THIS PROCESS AS MEDICINAL PRODUCTS, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.

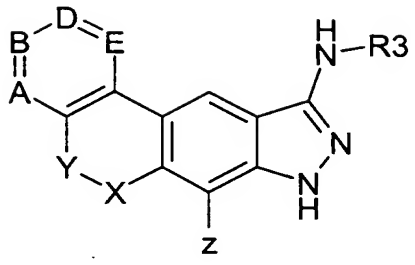
The present invention relates to the use of derivatives of formula (I) :



or the pharmaceutically acceptable salts thereof, as kinase inhibitors.

The invention relates to the use of the tetracyclic aminoindazole derivatives of formula (I) and the pharmaceutically acceptable salts thereof, for the preparation of pharmaceutical compositions for preventing and treating diseases that may result from an abnormal activity of kinases, such as, for example, those involved in neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, frontoparietal dementia, corticobasal degeneration, Pick's disease, strokes, cranial and spinal trauma and peripheral neuropathies, obesity, metabolic diseases, type II diabetes, essential hypertension, atherosclerotic cardiovascular diseases, polycystic ovary syndrome, syndrome X, immunodeficiency, cerebral ischemia and cancer, to the pharmaceutical compositions containing the novel tetracyclic aminoindazole derivatives and the pharmaceutically acceptable salts thereof, and to the novel tetracyclic aminoindazole derivatives and the pharmaceutically acceptable salts thereof.

The present invention relates to derivatives of formula (I) in which :



(I)

R3 represents a hydrogen or a group –C(O)-R4;

A, B, D and E represent, independently of one another, a CH or an N, in the knowledge that there are at most two nitrogens;

X represents a radical O, S, NR, CH_2, $(CH_2)_2$ or $(CH_2)_3$;

Y represents a radical CH_2, $(CH_2)_2$, CO, CS, (C=NH), O, S, NR, $C=CH_2$ or C-CHRa;

Z is a hydrogen or a halogen;

R4 is a $(C_1$-$C_6)$alkyl, aryl, aryl$(C_1$-$C_6)$alkyl, heteroaryl or heteroaryl$(C_1$-$C_6)$alkyl radical, an aryl or heteroaryl radical fused to a $(C_1$-$C_{10})$cycloalkyl radical, or a heterocyclic, cycloalkyl, adamantyl, polycycloalkyl, alkenyl or alkynyl radical; these radicals being optionally substituted with one or more substituents chosen from halogen, CN, NO_2, NH_2, OH, OR8, COOH, C(O)OR8, -O-C(O)R8, NR8R9, NHC(O)R8, C(O)NR8R9, SR8, S(O)R8, SO_2R8, $NHSO_2$R8, SO_2NR8R9, C(S)NR8R9, NHC(S)R8, -O-SO_2R8, -SO_2-O-R8, aryl, heteroaryl, formyl, trifluoromethyl, trifluoromethylsulfanyl and trifluoromethoxy;

Ra is a radical OH or OR;

R is a hydrogen or a $(C_1$-$C_6)$alkyl;

R8 and R9 are, independently of one another, a hydrogen, or $(C_1$-$C_6)$alkyl, aryl, alkenyl, alkynyl or heteroaryl, themselves optionally being substituted with one or more substituents chosen from halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, CN, NO_2, NH_2, OH, COOH, COOalkyl, $CONH_2$, formyl, trifluoromethyl and trifluoromethoxy;

the isomers thereof, the mixtures thereof, the racemic mixtures, enantiomers, diastereoisomers and tautomers thereof, and also the pharmaceutically acceptable salts thereof.

More particularly, the present invention relates to the use of the derivatives of formula (I) in which:

R3 represents a hydrogen or a group –C(O)-R4;

A and B independently represent a CH;

D and E represent, independently of one another, a CH or an N;

X represents a radical O or NR;

Y represents a radical CH_2, CO or $C{=}CH_2$;

Z is a halogen;

R4 is a (C_1-C_6)alkyl radical;

R is a hydrogen;

the isomers thereof, the mixtures thereof, the racemic mixtures, enantiomers, diastereoisomers and tautomers thereof, and also the pharmaceutically acceptable salts thereof.

In the definitions above and those which follow, the (C_1-C_6)alkyl radicals contain 1 to 6 carbon atoms in a straight or branched chain; the alkenyl radicals contain 2 to 6 carbon atoms and 1 to 3 conjugated or non-conjugated double bonds in a straight or branched chain; the alkynyl radicals contain 2 to 6 carbon atoms and 1 to 3 conjugated or non-conjugated triple bonds in a straight or branched chain; the aryl radicals are chosen from phenyl, naphthyl or indenyl; the heteroaryl radicals are 3- to 10-membered, optionally containing one or more hetero atoms chosen from oxygen, sulfur and nitrogen, in particular thiazolyl, thienyl, pyrrolyl, pyridyl, furyl, imidazolyl, oxazolyl, pyrazinyl, tetrazolyl, oxadiazolyl, thiadiazolyl, isoxadiazolyl,

isothiadiazolyl, isothiazolyl, isoxazolyl, triazolyl, pyrazolyl, indolyl; the halogen radical is either chlorine, iodine, fluorine or bromine; the polycycloalkyl radicals are chosen from adamantyl, quinuclidinyl, bornanyl, norbornanyl, bornenyl, norbornenyl; the heteroaryl radicals fused to a (C_1-C_{10})cycloalkyl are chosen from indanyl, isochromanyl, chromanyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydroquinolyl; the heterocyclic radicals contain 1 or 2 hetero atoms chosen from oxygen, sulfur and nitrogen and in particular represent piperidyl, morpholinyl, pyrrolidinyl, imidazolidinyl, pyrrazolidinyl, isothiazolidinyl, thiazolidinyl, isoxazolidinyl, oxazolidinyl, piperazinyl, azetidinyl, 2-piperidone, 3-piperidone, 4-piperidone, 2-pyrrolidone and 3-pyrrolidone.

The compounds of formula (I) have one or more asymmetric carbon atoms and can therefore be in the form of isomers, of a racemic mixture, of enantiomers and of diastereoisomers; these are also part of the invention as are mixtures thereof.

Among the compounds of formula (I) that are useful according to the invention, mention may be made of the following compounds :

N-[7-fluoro-5-methylene-5,8-dihydro-6-oxa-8,9-diazacyclopenta[b]phenanthren-10-yl)butyramide

N-[7-fluoro-5,8-dihydro-6-oxa-8,9-diazacyclopenta[b]phenanthren-10-yl)butyramide

N-[7-fluoro-5-oxo-5,8-dihydro-6H-6,8,9-triazacyclopenta[b]phenanthren-10-yl)butyramide

N-[7-fluoro-5,8-dihydro-6-oxa-1,8,9-triazacyclopenta[b]phenanthren-10-yl)butyramide

N-[7-fluoro-5,8-dihydro-6-oxa-2,8,9-triazacyclopenta[b]phenanthren-10-yl)butyramide

7-Fluoro-5,8-dihydro-6-oxa-8,9-diazacyclopenta[b]-phenanthren-10-ylamine

the isomers thereof, the mixtures thereof, the racemic mixtures, enantiomers, diastereoisomers and tautomers thereof, and also the pharmaceutically acceptable salts thereof.

The invention also relates to the pharmaceutical compositions containing, as active principle, a derivative of formula (I) for which

R3 represents a hydrogen or a group –C(O)-R4;

A, B, D and E represent, independently of one another, a CH or an N, in the knowledge that there are at most two nitrogens;

X represents a radical O, S, NR, CH_2, $(CH_2)_2$ or $(CH_2)_3$;

Y represents a radical CH_2, $(CH_2)_2$, CO, CS, (C=NH), O, S, NR, $C=CH_2$ or C-CHRa;

Z is a hydrogen or a halogen;

R4 is a $(C_1$-$C_6)$alkyl, aryl, aryl$(C_1$-$C_6)$alkyl, heteroaryl or heteroaryl$(C_1$-$C_6)$alkyl radical, an aryl or heteroaryl radical fused to a $(C_1$-$C_{10})$cycloalkyl radical, or a heterocyclic, cycloalkyl, adamantyl, polycycloalkyl, alkenyl or alkynyl radical; these radicals being optionally substituted with one or more substituents chosen from halogen, CN, NO_2, NH_2, OH, OR8, COOH, C(O)OR8, -O-C(O)R8, NR8R9, NHC(O)R8, C(O)NR8R9, SR8, S(O)R8, SO_2R8, $NHSO_2$R8, SO_2NR8R9, C(S)NR8R9, NHC(S)R8, -O-SO_2R8, -SO_2-O-R8, aryl, heteroaryl, formyl, trifluoromethyl, trifluoromethylsulfanyl and trifluoromethoxy;

Ra is a radical OH or OR;

R is a hydrogen or a $(C_1$-$C_6)$alkyl;

R8 and R9 are, independently of one another, a hydrogen, or $(C_1$-$C_6)$alkyl, aryl, alkenyl, alkynyl or heteroaryl, themselves optionally being substituted with one or

more substituents chosen from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, CN, NO_2, NH_2, OH, COOH, COOalkyl, $CONH_2$, formyl, trifluoromethyl and trifluoromethoxy;

the isomers thereof, the mixtures thereof, the racemic mixtures, enantiomers, diastereoisomers and tautomers thereof, and also the pharmaceutically acceptable salts thereof.

More particularly, the present invention relates to the use, as medicinal product, of the tetracyclic aminoindazole derivatives of formula (I) in which:

R3 represents a hydrogen or a group –C(O)-R4;

A, B, D and E represent, independently of one another, a CH or an N, in the knowledge that there are at most two nitrogens;

X represents a radical O, S, NR, CH_2, $(CH_2)_2$ or $(CH_2)_3$;

Y represents a radical CH_2, $(CH_2)_2$, CO, CS, (C=NH), O, S, NR, $C=CH_2$ or C-CHRa;

Z is a hydrogen or a halogen;

R4 is a (C_1-C_6)alkyl, aryl, aryl(C_1-C_6)alkyl, heteroaryl or heteroaryl(C_1-C_6)alkyl radical, an aryl or heteroaryl radical fused to a (C_1-C_{10})cycloalkyl radical, or a heterocyclic, cycloalkyl, adamantyl, polycycloalkyl, alkenyl or alkynyl radical; these radicals being optionally substituted with one or more substituents chosen from halogen, CN, NO_2, NH_2, OH, OR8, COOH, C(O)OR8, -O-C(O)R8, NR8R9, NHC(O)R8, C(O)NR8R9, SR8, S(O)R8, SO_2R8, $NHSO_2$R8, SO_2NR8R9, C(S)NR8R9, NHC(S)R8, -O-SO_2R8, -SO_2-O-R8, aryl, heteroaryl, formyl, trifluoromethyl, trifluoromethylsulfanyl and trifluoromethoxy;

Ra is a radical OH or OR;

R is a hydrogen or a (C_1-C_6)alkyl;

R8 and R9 are, independently of one another, a hydrogen, or (C_1-C_6)alkyl, aryl, alkenyl, alkynyl or heteroaryl, themselves optionally being substituted with one or

more substituents chosen from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, CN, NO_2, NH_2, OH, COOH, COOalkyl, $CONH_2$, formyl, trifluoromethyl and trifluoromethoxy;

the isomers thereof, the mixtures thereof, the racemic mixtures, enantiomers, diastereoisomers and tautomers thereof, and also the pharmaceutically acceptable salts thereof.

And preferably, the present invention relates to the use, as medicinal product, of the tetracyclic aminoindazole derivatives of formula (I) in which:

R3 represents hydrogen or a group –C(O)-R4;

A and B independently represent a CH;

D and E represent, independently of one another, a CH or an N;

X represents a radical O or NR;

Y represents a radical CH_2, CO or $C=CH_2$;

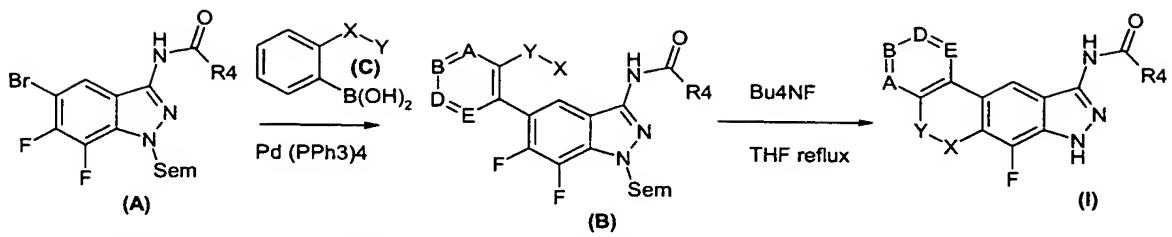
Z is a halogen;

R4 is a (C_1-C_6)alkyl radical;

R is a hydrogen;

the racemic mixtures, mixtures, enantiomers and diastereoisomers thereof and the mixtures thereof, the tautomers thereof and the pharmaceutically acceptable salts thereof.

The derivatives of formula (B) (I) can be obtained from products described in patent applications WO 03/078403, WO 04/022544 and PCT/FR03/02634 according to the following scheme :

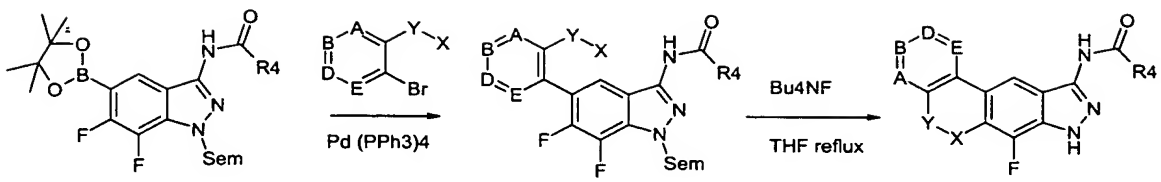


The method involves Suzuki-type coupling. Compound **A**, intermediate obtained as described in patent applications WO 03/078403, WO 04/022544 and PCT/FR03/02634, reacts with a boronic acid, an alkyl or cycloalkyl boronate, or a (hetero)aryldialkyl boron of formula **C**. The reaction is carried out under an inert atmosphere in the presence of an inorganic base such as K_3PO_4 , Na_2CO_3 or $Ba(OH)_2$, of a palladium salt (catalyst) such as bistriphenylphosphinodichloropalladium ($PdCl_2(PPh_3)_2$), tetrakistriphenylphosphine palladium ($Pd(PPh_3)_4$) or diphenylphosphinoferrocene palladium ($PdCl_2$dppf), in a solvent such as dimethylformamide, dimethoxyethane, tetrahydrofuran, dioxane, toluene, xylene or ethanol, optionally in the presence of water, at a temperature of between 20°C and the boiling point of the reaction medium (Kotha S. et al., Tetrahedron, 2002, *58*, 9633).

The intermediate of formula B is cyclized and deprotected in the presence of 6 to 10 equivalents of tetrabutylammonium fluoride at the reflux, for 2 to 10 hours, or of tetrahydrofuran.

The boronic acids, alkyl or cycloalkyl boronates or (hetero)aryldialkyl boron are commercial or are obtained by use or adaptation of methods described in the literature, for example in Kabalka G.W. et al., Tetrahedron Letters 1986, *27*, 3843, Nicoud J.F. et al., Tetrahedron Letters 1993, *34*, 8237, Tour J.M. et al., J. Amer. Chem. Soc. 1994, *116*, 11723, or Mueller T.J.J. et al., Synthesis 2002, *9*, 1163.

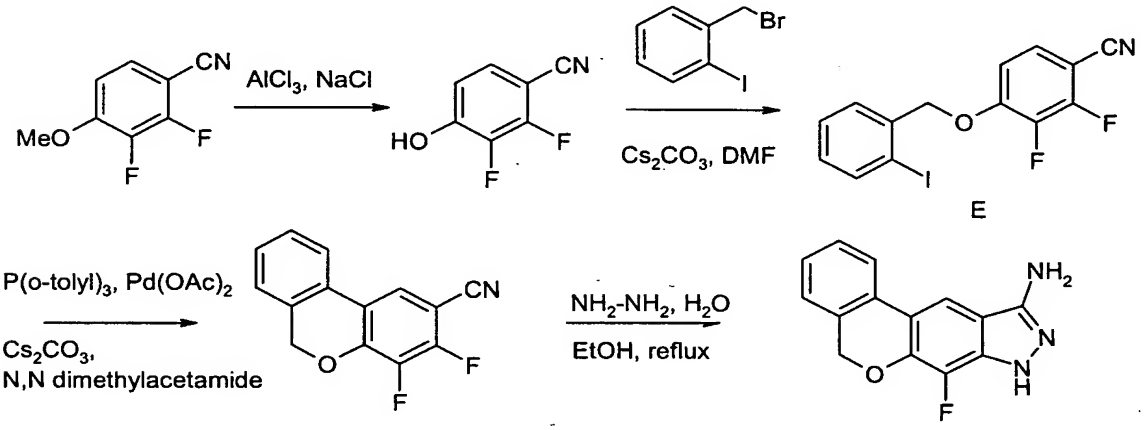
Another route for obtaining these compounds is to follow the synthesis scheme below :



D

The boronic ester **D** is obtained by a Miyaura reaction, which consists in reacting a halogenated derivative with bis(pinacolato)diborane according to Ishiyama et al., J. Org. Chem., *60*, 7508, (1995). The reaction is carried out in the presence of $Pd(dba)_2$ and PCy_3 in the presence of potassium acetate in dioxane at 80°C. The remainder of the reactions are carried out as described previously and according to the methods described in patent applications WO 03/078403, WO 04/022544 and PCT/FR03/02634.

A third route for obtaining compounds where R4 is a hydrogen is as follows :



E F G

This reaction of intramolecular cyclization of compound E so as to give the compound **F** consists in reacting an aryl halide with an arene and is a reaction of aromatic substitution in the presence of a palladium salt. (V.H. Rawald, J. Org. Chem., 2, (1997); D. Ames, Synthesis, 234, (1983); J.Y. Merour, *41*, 1987, (1995), S. Kotha, Tetrahedron, *58*, 9633-95, (2002). The reaction is carried out under an inert atmosphere in the presence of an organic base such as K_3PO_4 , Na_2CO_3 or $Ba(OH)_2$, of a palladium salt (catalyst) such as bistriphenylphosphinodichloropalladium ($PdCl_2(PPh_3)_2$), tetrakistriphenylphosphine palladium ($Pd(PPh_3)_4$) or

diphenylphosphinoferrocene palladium ($PdCl_2dppf$), in a solvent such as dimethylformamide, dimethoxyethane, tetrahydrofuran, dioxane, toluene, xylene or ethanol, optionally in the presence of water, at a temperature of between 20°C and the boiling point of the reaction medium, and more particularly, in our case, Cs_2CO_3, tri-ortho-tolylphosphine, palladium acetate at the reflux of N,N-dimethylacetamide, D. Hennings, J. Org. Chem., *62*, 2-3, (1997).

Compound **E** is obtained by means of a Williamson reaction, which consists in reacting an alkoxide or a phenate, prepared from an alcohol or from a phenol, with an alkyl halide, G. N. Vyas et al., Org. Synth., Collect. Vol IV, 836, (1963); A. R. MacKenzie, Tetrahedron, *42*, 3259, (1986). For a general review, H. Feuer, J. Hooz, The Chemistry of Ether Linkage, pages 446-468, Pataï Editeur, Interscience Publishers, London, New-York, Sydney, 1967.

The 3-amino-1H-indazoles of formula G can be obtained by reacting a 2-fluoro-benzonitrile with hydrazine hydrate or hydrochloride at reflux for 2 to 18 hours in an alcohol of the ethanol or n-butanol type according to R.F. Kaltenbach, Bioorg. Med. Chem. Lett., 9,(15), 2259-62, (1999).

The compounds of formula (I) are isolated and can be purified by the conventional known methods, for example by crystallization, chromatography or extraction.

The compounds of formula (I) can be optionally converted into addition salts with an inorganic or organic acid by means of the action of such an acid in an organic solvent such as an alcohol, a ketone, an ether or a chlorinated solvent. These salts are also part of the invention.

The following salts may be mentioned as examples of pharmaceutically acceptable salts : benzenesulfonate, hydrobromide, hydrochloride, citrate, ethanesulfonate, fumarate, gluconate, iodate, maleate, isoethionate, methanesulfonate, methylenebis-b-oxynaphthoate, nitrate, oxalate, pamoate, phosphate, salicylate, succinate, sulfate, tartrate, theophyllinacetate and p-toluenesulfonate.

The compounds of formula (I) are kinase inhibitors and are thus useful for the prevention and treatment of neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, frontoparietal dementia, corticobasal degeneration, Pick's disease, strokes, cranial and spinal trauma and peripheral neuropathies, obesity, essential hypertension, atherosclerotic cardiovascular diseases, polycystic ovary syndrome, syndrome X, immunodeficiency and cancer.

Their activities have been determined by measuring the inhibition of phosphorylation of the tau protein in adult rat cortex sections.

The 300 μm-thick cortex sections are prepared from 8-to-10-week-old male OFA rats (Iffa-Credo) sacrificed by decapitation. They are incubated in 5 ml of DMEM medium containing pyruvate and 4.5 g/l glucose at 37°C for 40 min. The sections are then washed twice with the medium, distributed in microtubes (50 μl in 500 μl of medium with or without test compounds) and incubated at 37°C with stirring. Two hours later, the experiment is stopped by centrifugation. The sections are lysed, sonified and centrifuged at 18 300 g for 15 min at 4°C. The protein concentration in the supernatant is determined by means of a commercial assay (BCA Protein Assay, Pierce) based on the Lowry method.

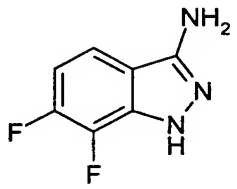
The samples, denatured beforehand for 10 min at 70°C, are prepared on a 4-12% bis-tris vertical gel in the presence of MOPS-SDS buffer and electrotransferred onto a nitrocellulose membrane. The immunolabeling is carried out with the AD2 monoclonal antibody which recognizes specifically the phosphorylated epitopes Ser396/404 of the tau protein. The immunoreactive proteins are visualized by adding a second antibody directed against mouse IgGs and coupled to peroxidase, and a chemiluminescent substrate. The autoradiograms obtained are, finally, quantified using the 'GeneTools' program from Syngene (GeneGnome, Ozyme) so as to determine an IC_{50}.

The compounds of formula (I) exhibit a very advantageous activity and, in particular, some compounds have an IC_{50} of less than 100 μM.

The following examples illustrate the invention in a nonlimiting manner.

EXAMPLE 1

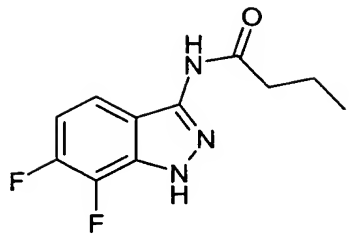
6,7-difluoro-1H-indazol-3-amine:



0.32 cm^3 of hydrazine monohydrate is added to 0.46 cm^3 of 2,3,4-trifluorobenzonitrile in 10 cm^3 of absolute ethanol. The medium is heated at around 75°C for 17 hours and then 10 cm^3 of ethyl acetate, 5 cm^3 of tetrahydrofuran and 5 cm^3 of distilled water are added. The organic phase is separated by settling out and re-washed with 10 cm^3 of distilled water and then with 10 cm^3 of a saturated aqueous sodium chloride solution. The organic phase is separated by settling out, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 50°C). The residue obtained is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 1.5 cm), elution being carried out with a cyclohexane/ethyl acetate (50/50 by volume) mixture. The fractions containing the expected product are combined and then evaporated under reduced pressure (2 kPa; 40°C); after drying (90 Pa; 40°C), 100 mg of 6,7-difluoro-1H-indazol-3-amine are obtained in the form of a white solid which melts at 183°C.

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 5.57 (unresolved peak : 2H); 6.93 (unresolved peak : 1H); 7.52 (ddd, J = 8.5 – 4.5 and 1 Hz : 1H); 12.01 (unresolved peak : 1H).

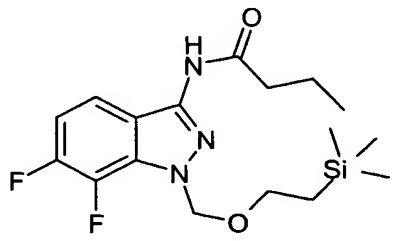
N-(6,7-difluoro-1H-indazol-3-yl)butanamide:



0.61 cm^3 of butyryl chloride is added, after having cooled to around 3°C, to 1 g of 6,7-difluoro-1H-indazol-3-amine described above, in 15 cm^3 of pyridine and the mixture is then left at ambient temperature for 76 hours. The reaction medium is concentrated under reduced pressure (2 kPa; 40°C) and the residue is taken up with 25 cm^3 of ethyl acetate and with 25 cm^3 of water. The organic phase is washed with 25 cm^3 of distilled water and then with 25 cm^3 of a saturated aqueous sodium chloride solution. After drying over magnesium sulfate, filtration and concentration under reduced pressure (2 kPa; 40°C), the residue obtained is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 3 cm), elution being carried out with a dichloromethane/methanol (98/2 by volume) mixture. The fractions containing the expected product are combined and then evaporated under reduced pressure (2 kPa; 40°C); after drying (90 Pa; 40°C), 596 mg of N-(6,7-difluoro-1H-indazol-3-yl)butanamide are obtained in the form of a white solid which melts at 191°C.

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 0.97 (t, J = 7.5 Hz : 3H); 1.67 (mt : 2H); 2.40 (t, J = 7 Hz : 2H); 7.10 (mt : 1H); 7.63 broad dd, J = 9 and 4.5 Hz : 1H); 10.47 (broad unresolved peak : 1H); 13.35 (broad unresolved peak : 1H).

N-(6,7-difluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl)butanamide

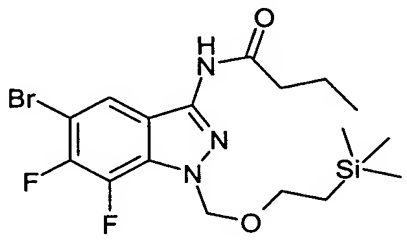


A solution of 1.1 g of N-(6,7-difluoro-1H-indazol-3-yl)butanamide in 180 cm^3 of dimethylformamide is added dropwise, over 3 hours, to 1.65 g of sodium hydride at 60% in oil, in 50 cm^3 of dimethylformamide. The reaction medium is concentrated to dryness under reduced pressure and taken up with 250 cm^3 of ethyl acetate and 200 cm^3 of water; the organic phase is separated by settling out, washed with 150 cm^3 of water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 50°C). The crude is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 6 cm), elution being carried out with a cyclohexane/ethyl acetate (80/20 by volume) mixture. The fractions containing the expected product are combined and evaporated under reduced pressure (2 kPa; 50°C) so as to give 7.3 g of N-[6,7-difluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide in the form of a yellow oil.

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : - 0.09 (s : 9H); 0.82 (t, J = 8 Hz : 2H); 0.96 (t, J = 7.5 Hz : 3H); 1.67 (mt : 2H); 2.41 (t, J = 7 Hz : 2H); 3.56 (t, J = 8 Hz : 2H); 5.66 (s : 2H); 7.22 (ddd, J = 11 – 9 and 7 Hz : 1H); 7.69 (broad dd, J = 9 and 4.5 Hz : 1H); 10.60 (unresolved peak : 1H).

EI mass spectrum m/z = 369 M+

N-(5-bromo-6,7-difluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl)-butanamide



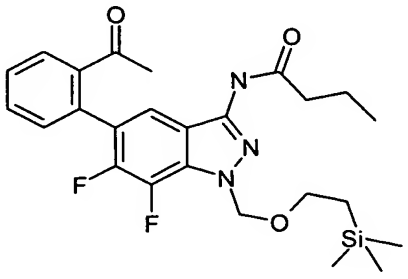
0.87 cm^3 of pyridine is added to 1 g of N-[6,7-difluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide described above in 30 cm^3 of chloroform, followed by 0.56 cm^3 of bromine, and the mixture is refluxed overnight.

50 cm^3 of dichloromethane and 50 cm^3 of an aqueous 10% sodium thiosulfate solution are added to the reaction medium. After stirring for 10 minutes, the insoluble material is removed by filtration through sintered glass and the organic phase is washed with 50 cm^3 of water and with 50 cm^3 of a saturated sodium chloride solution. The organic phase is separated by settling out, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 45°C). The crude, 1.1 g, is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 μm; diameter 3 cm), elution being carried out with a cyclohexane/ethyl acetate (90/10 by volume) mixture. The fractions containing the expected product are combined and evaporated under reduced pressure (2 kPa; 50°C). After drying (90 Pa; 45°C), 230 mg of N-(5-bromo-6,7-difluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl)butanamide are obtained in the form of a colorless oil.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : - 0.05 (s : 9H); 0.84 (t, J = 8 Hz : 2H); 0.95 (t, J = 7.5 Hz : 3H); 1.66 (mt : 2H); 2.43 (t, J = 7 Hz : 2H); 3.59 (t, J = 8 Hz : 2H); 5.69 (s : 2H); from 7.40 to 7.65 (mt : 5H); 7.82 (broad d, J = 7 Hz : 1H); 10.64 (unresolved peak : 1H).

EI mass spectrum m/z = 447 M+.

N-[6,7-difluoro-5-(2-acetylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide



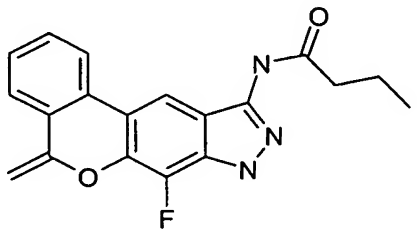
494 mg of 2-acetylphenylboronic acid, 596 mg of sodium carbonate in 25 cm^3 of water and 297 mg of tetrakistriphenylphosphine palladium are added to 0.9 g of N-(5-

bromo-6,7-difluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl)butanamide, prepared above, in 120 cm^3 of dioxane, and the mixture is refluxed for 2 hours. The reaction medium is diluted with 100 cm^3 of ethyl acetate, washed with 2 times 100 cm^3 of water and 75 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 50°C). The crude obtained is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 3.5 cm), elution being carried out with a cyclohexane/ethyl acetate (80/20 by volume) mixture. The fractions containing the expected product are combined, evaporated under reduced pressure (2 kPa; 50°C) and dried (90 kPa, 45°C), so as to give 0.95 g of N-[6,7-difluoro-5-(2-acetylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide in the form of a greenish yellow oil.

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : - 0.05 (s : 9H); 0.86 (t, J = 8 Hz : 2H); 0.94 (t, J = 7 Hz : 3H); 1.64 (mt : 2H); 2.40 (broad t, J = 7.5 Hz : 2H); 2.47 (s : 3H); 3.61 (t, J = 8 Hz : 2H); 5.69 (s : 2H); 7.44 (broad d, J = 7.5 Hz : 1H); from 7.55 to 7.75 (mt : 3H); 7.95 (broad d, J = 7.5 Hz : 1H); 10.63 (unresolved peak : 1H).

EI mass spectrum : m/z=487 [M+.],

N-[7-fluoro-5-methylene-5,8-dihydro-6-oxa-8,9-diazacyclopenta[b]phenanthren-10-yl)butyramide



11.7 cm^3 of tetrabutylammonium fluoride in 1M solution in tetrahydrofuran are added to 0.95 g of N-[6,7-difluoro-5-(2-acetylphenyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide described above, in 75 cm^3 of tetrahydrofuran, and the

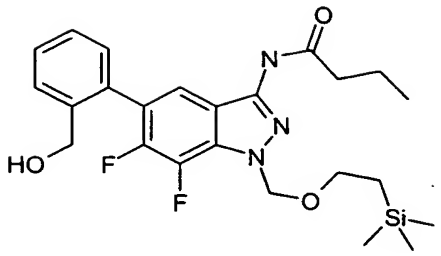
mixture is refluxed for 18 hours; since the reaction is incomplete, 7.8 cm^3 of the tetrabutylammonium fluoride solution are again added and the reflux is continued for 18 hours. After cooling, 100 cm^3 of ethyl acetate and 75 cm^3 of a saturated sodium hydrogen carbonate solution are added. The organic phase is separated by settling out and washed with 75 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa; 50°C) so as to give a crude which is purified by chromatography under an argon pressure of 50 KPa, on a column of silica gel (mean particle size 40-60 µm; diameter 3 cm), elution being carried out with a cyclohexane/ethyl acetate (70/30 by volume) mixture. The fractions containing the expected product are combined and evaporated under reduced pressure (2 kPa; 50°C); the solid obtained is taken up with 10 cm^3 of diisopropyl ether, filtered through sintered glass, washed with 2 times 1.5 cm^3 of ethyl acetate and 10 cm^3 of diisopropyl ether and then dried (90 Pa; 45°C), so as to give 60 mg of N-[7-fluoro-5-methylene-5,8-dihydro-6-oxa-8,9-diazacyclopenta[b]phenanthren-10-yl)butyramide in the form of a pinkish white solid which melts at 200°C.

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 0.99 (broad t, J = 7 Hz : 3H); 1.70 (mt : 2H); 2.44 (broad t, J = 7.5 Hz : 2H); 4.89 (broad d, J = 2 Hz : 1H); 5.30 (broad d, J = 2 Hz : 1H); 7.40 (broad t, J = 7.5 Hz : 1H); 7.55 (broad t, J = 7.5 Hz : 1H); 7.85 (broad d, J = 7.5 Hz : 1H); 7.95 (broad d, J = 7.5 Hz : 1H); 8.27 (broad s : 1H); 10.45 (unresolved peak : 1H); from 12.90 to 13.30 (broad unresolved peak : 1H)

EI mass spectrum : m/z=337 [M+], m/z=267 (base peak), m/z=238

EXAMPLE 2

N-[6,7-difluoro-5-(2-hydroyphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide

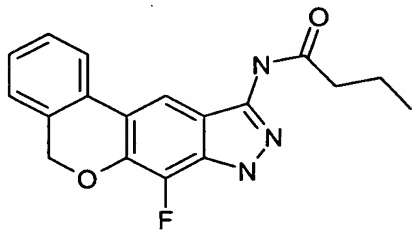


508 mg of 2-hydroxymethylphenylboronic acid, 662 mg of sodium carbonate in 30 cm^3 of water and 330 mg of tetrakistriphenylphosphine palladium are added to 1.0 g of N-(5-bromo-6,7-difluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl)butanamide, prepared above, in 130 cm^3 of dioxane, and the mixture is refluxed for 2 hours. The reaction medium is filtered through celite, rinsed with 100 cm^3 of ethyl acetate, separated by settling out, washed with 100 cm^3 of water and 75 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 50°C); 1.5 g of crude are obtained. The crude obtained is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 μm; diameter 3.5 cm), elution being carried out with a cyclohexane/ethyl acetate (50/50 by volume) mixture. The fractions containing the expected product are combined, evaporated under reduced pressure (2 kPa; 50°C) and dried (90 Pa, 45°C), so as to give 1.19 g of N-[6,7-difluoro-5-(-(2-hydroxymethylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide in the form of a green oil.

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : - 0.05 (s : 9H); 0.86 (t, J = 8 Hz : 2H); 0.93 (t, J = 7 Hz : 3H); 1.63 (mt : 2H); 2.40 (broad t, J = 7.5 Hz : 2H); 3.61 (t, J = 8 Hz : 2H); 4.36 (d, J = 5.5 Hz : 2H); 5.13 (t, J = 5.5 Hz : 1H); 5.70 (broad s : 2H); 7.26 (broad d, J = 7.5 Hz : 1H); 7.38 (ddt, J = 7.5 and 1.5 Hz : 1H); 7.49 (ddt, J = 7.5 and 1.5 Hz : 1H); 7.63 (broad d, J = 7.5 Hz : 1H); 7.66 (broad d, J = 6 Hz : 1H); 10.62 (unresolved peak : 1H).

EI mass spectrum : m/z=374 [M+. - H], m/z=111, m/z=98 (base peak), m/z=91

N-[7-fluoro-5,8-dihydro-6-oxa-8,9-diazacyclopenta[b]phenanthren-10-yl)butyramide



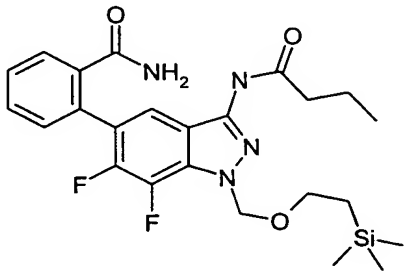
11.4 cm^3 of tetrabutylammonium fluoride in 1M solution in tetrahydrofuran are added to 1.06 g of N-[6,7-difluoro-5-(2-hydroxymethylphenyl-1-[[2-(trimethylsilyl)ethoxy]méthyl]-1H-indazol-3-yl]butanamide described above, in 50 cm^3 of tetrahydrofuran, and the mixture is refluxed for 18 hours. After cooling, 100 cm^3 of ethyl acetate are added and the mixture is washed with 2 times 75 cm^3 of a saturated sodium hydrogen carbonate solution; the organic phase is separated by settling out and washed with 75 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa; 50°C) so as to give 1.3 g of crude which is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (particle size 40-60 µm; diameter 3.5 cm), elution being carried out with a cyclohexane/ethyl acetate (80/20 by volume) mixture. The fractions containing the expected product are combined and evaporated under reduced pressure (2 kPa; 50°C), so as to give 0.30 g of solid which is taken up with 10 cm^3 of diisopropyl ether, filtered through sintered glass, washed with 2 times 10 cm^3 of diisopropyl ether and then dried (90 Pa; 45°C); 0.10 g of N-[7-fluoro-5,8-dihydro-6-oxa-8,9-diazacyclopenta[b]phenanthren-10-yl)butyramide in the form of white crystals which melt at 225°C.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 0.99 (t, J = 7 Hz : 3H); 1.71 (mt : 2H); 2.44 (t, J = 7.5 Hz : 2H); 5.23 (broad s : 2H); 7.36 (mt : 2H); 7.48 (mt : 1H); 7.80 (broad d, J = 7.5 Hz : 1H); 8.14 (broad s : 1H); 10.43 (unresolved peak : 1H); from 12.95 to 13.15 (unresolved peak : 1H).

EI mass spectrum : m/z=518 [M+], m/z=342, m/z=252 (base peak)

EXAMPLE 3

N-[6,7-difluoro-5-(2-aminocarbonylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide

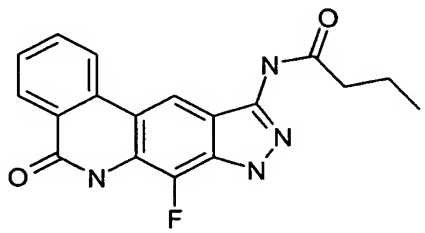


552 mg of 2-aminocarbonylphenylboronic acid, 662 mg of sodium carbonate in 25 cm^3 of water and 330 mg of tetrakistriphenylphosphine palladium are added to 1.0 g of N-(5-bromo-6,7-difluoro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl)butanamide, prepared above, in 130 cm^3 of dioxane, and the mixture is refluxed for 3 hours. 100 cm^3 of ethyl acetate are added, and the mixture is separated by settling out, washed with 100 cm^3 of water and 100 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 50°C). 1.3 g of crude are obtained. The crude obtained is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 3.5 cm), elution being carried out with a cyclohexane/ethyl acetate (70/30 by volume) mixture. The fractions containing the expected product are combined, evaporated under reduced pressure (2 kPa; 50°C) and dried (90 Pa, 45°C), so as to give 1.0 g of N-[6,7-difluoro-5-(2-aminocarbonylphenyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide in the form of a white foam.

^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : - 0.04 (s : 9H); 0.88 (t, J = 8 Hz : 2H); 0.94 (t, J = 7 Hz : 3H); 1.64 (mt : 2H); 2.40 (broad t, J = 7.5 Hz : 2H); 3.61 (t, J = 8 Hz : 2H); 5.68 (broad s : 2H); 7.23 (broad s : 1H); 7.40 (broad dd, J = 7.5 and 1 Hz : 1H); from 7.45 to 7.70 (mt : 4H); 7.77 (broad s : 1H); 10.60 (unresolved peak : 1H).

EI mass spectrum : m/z=488 [M+], m/z=371, m/z=360, m/z=301, m/z=73 (base peak), m/z=43

N-[7-fluoro-5-oxo-5,8-dihydro-6H-6,8,9-triazacyclopenta[b]phenanthren-10-yl)-butyramide



12.3 cm^3 of tetrabutylammonium fluoride in 1M solution in tetrahydrofuran are added to 1.0 g of N-[6,7-difluoro-5-(2-hydroxymethylphenyl-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide described above, in 50 cm^3 of tetrahydrofuran, and the mixture is refluxed for 18 hours. After cooling, 100 cm^3 of ethyl acetate are added, and the mixture is washed with 100 cm^3 of saturated sodium hydrogen carbonate solution; the organic phase is separated by settling out and washed with 100 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa; 50°C) so as to give a crude which is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 3.5 cm), elution being carried out with a cyclohexane/ethyl acetate (80/20 by volume) mixture and then with a methylene chloride/methanol (97/3 by volume) mixture. The fractions containing the expected product are combined and evaporated under reduced pressure (2 kPa; 50°C), so as to give 1.7 g of solid which is purified again by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 3.5 cm), elution being carried out with a methylene chloride/methanol (95/5 by volume) mixture. The fractions containing the expected product are combined and evaporated under reduced pressure (2 kPa; 50°C), and the solid obtained is taken up with 10 cm^3 of ethyl acetate, filtered through sintered glass, washed with 2 times 10 cm^3 of ethyl acetate and 20 cm^3 of diisopropyl

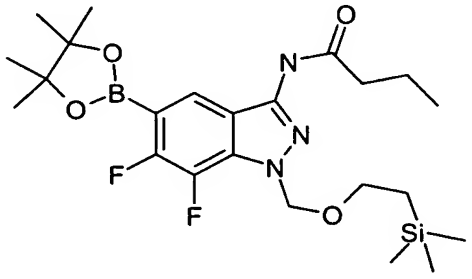
ether and then dried (90 Pa; 45°C), so as to give 0.14 g of N-[7-fluoro-5-oxo-5,8-dihydro-6H-6,8,9-triazacyclopenta[b]phenanthren-10-yl)butyramide in the form of beige-white crystals which melt at more than 260°C.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 1.01 (broad t, J = 7 Hz : 3H); 1.73 (mt : 2H); 2.48 (broad t, J = 7.5 Hz : 2H); 7.65 (broad t, J = 7.5 Hz : 1H); 7.90 (broad t, J = 7.5 Hz : 1H); 8.33 and 8.37 (2 broad d, J = 7.5 Hz : 2H in total); 8.72 (broad s : 1H); 10.54 (unresolved peak : 1H); 11.55 (broad s : 1H); 13.16 (broad s : 1H).

EI mass spectrum : m/z=338 [M+], m/z=268 (base peak)

EXAMPLE 4

N-[6,7-difluoro-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide:



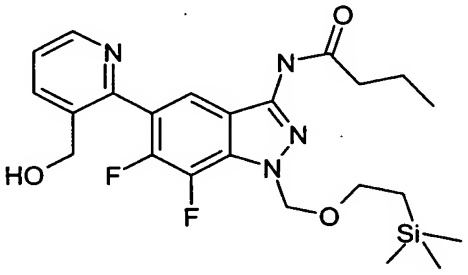
4.7 g of bis(pinacolato)diborane, 2.27 g of potassium acetate and then 257 mg of bis(dibenzylidene acetone) palladium and, finally, 302 mg of tricyclohexylphosphine are added to 6.9 g of N-[6,7-difluoro-5-bromo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl)butanamide described above, in 200 cm^3 of dioxane. The medium is brought to reflux for 2 hours and then allowed to return to ambient temperature, filtered through sintered glass covered with celite, rinsed with 3 times 200 cm^3 of ethyl acetate, separated by settling out, and the organic phase is washed with 2 times 200 cm^3 of water and then with 200 cm^3 of a saturated sodium chloride solution. The organic phase is dried over magnesium sulfate, filtered, and then concentrated to dryness under reduced pressure (2 kPa; 45°C) so as to give 12 g of a brown oil. The

crude is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 μm; diameter 4.5 cm), elution being carried out with a cylohexane/ethyl acetate (80/20 by volume) mixture. The fractions containing the expected product are combined and evaporated under reduced pressure (2 kPa; 50°C), so as to give 7.5 g of N-[6,7-difluoro-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide in the form of a yellow oil.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : - 0.10 (s : 9H); 0.81 (t, J = 8 Hz : 2H); 0.95 (t, J = 7 Hz : 3H); 1.33 (s : 12H); 1.66 (mt : 2H); 2.42 (t, J = 7.5 Hz : 2H); 3.55 (t, J = 8 Hz : 2H); 5.64 (broad s : 2H); 8.10 (broad d, J = 5 Hz : 1H); 10.62 (unresolved peak : 1H).

EI mass spectrum : m/z=495 [M+],

N-[6,7-difluoro-5-(3-hydroxyméthyl-2-pyridinyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide :



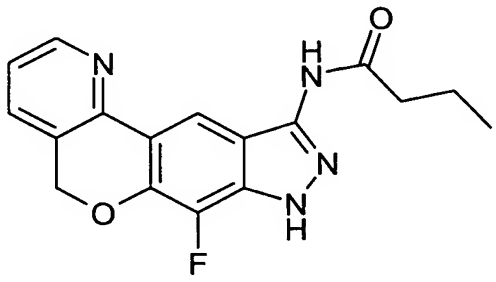
0.68 g of 2-bromo-3-hydroxymethylpyridine prepared according to Ashimori Atsuyuki, Chemical & Pharmaceutical Bulletin, 38, 2446-58, (1990), 25 cm^3 of water, 600 mg of sodium carbonate and 300 mg of tetrakistriphenylphosphine palladium are added to 1 g of N-[6,7-difluoro-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide described above, in 120 cm^3 of dioxane. The medium is then brought to reflux for 4 hours and then allowed to return to ambient temperature and 200 cm^3 of ethyl acetate are added. The organic phase is washed twice with 150 cm^3 of

distilled water and then with 100 cm^3 of a saturated aqueous sodium chloride solution, then dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 45°C) so as to give 2.5 g of yellow oil. The residue is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 3.5 cm), elution being carried out with a cyclohexane/ethyl acetate (50/50 by volume) mixture. The fractions containing the expected product are combined and evaporated under reduced pressure (2 kPa; 50°C). 0.85 mg of N-[6,7-difluoro-5-(3-hydroxymethyl-2-pyridinyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide is obtained in the form of a yellow oil.

^1H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm) : - 0.07 (s : 9H); 0.86 (t, J = 8 Hz : 2H); 0.92 (t, J = 7 Hz : 3H); 1.63 (mt : 2H); 2.39 (broad t, J = 7.5 Hz : 2H); 3.60 (t, J = 8 Hz : 2H); 4.40 (d, J = 5.5 Hz : 2H); 5.34 (t, J = 5.5 Hz : 1H); 5.71 (s : 2H); 7.52 (dd, J = 8 and 5 Hz : 1H); 7.75 (broad d, J = 6 Hz : 1H); 8.03 (dd, J = 8 and 1.5 Hz : 1H); 8.59 (dd, J = 5 and 1.5 Hz : 1H); 10.66 (unresolved peak : 1H).

ES+ mass spectrum : m/z=477 [MH+]

N-[7-fluoro-5,8-dihydro-6-oxa-1,8,9-triazacyclopenta[b]phenanthren-10-yl)-butyramide



10.7 cm^3 of tetrabutylammonium fluoride in 1M solution in tetrahydrofuran are added to 0.85 mg of N-[6,7-difluoro-5-(3-hydroxymethyl-2-pyridinyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide described above, in 75 cm^3 of tetrahydrofuran, and the reaction medium is then brought to reflux for 18

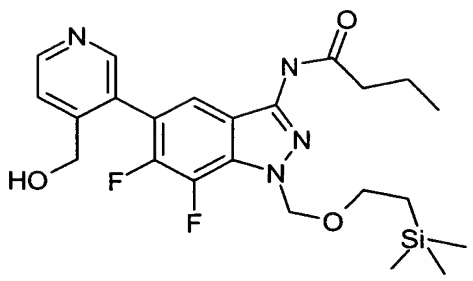
hours and subsequently allowed to return to ambient temperature in order to add 100 cm^3 of ethyl acetate. The organic phase is washed with 100 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and then with 100 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 45°C) so as to give 1.2 g of brown oil. The residue is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 3.5 cm), elution being carried out with a cyclohexane/ethyl acetate (30/70 by volume) mixture. The fractions containing the expected product are combined and concentrated to dryness under reduced pressure (2 kPa; 50°C). The residue is taken up with 20 cm^3 of diisopropyl ether, filtered through sintered glass and then washed successively with 10 cm^3 of diisopropyl ether, with 4 times 4 cm^3 of ethyl acetate and, finally, with 10 cm^3 of diisopropyl ether. After drying (90 Pa; 50°C), 0.18 g of N-[7-fluoro-5,8-dihydro-6-oxa-1,8,9-triazacyclopenta[b]phenanthren-10-yl)butyramide is obtained in the form of cream crystals which melt at 218°C.

^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 0.98 (t, J = 7 Hz : 3H); 1.69 (mt : 2H); 2.43 (t, J = 7.5 Hz : 2H); 5.37 (s : 2H); 7.36 (dd, J = 7.5 and 5 Hz : 1H); 7.74 (broad dd, J = 7.5 and 1.5 Hz : 1H); 8.52 (broad s : 1H); 8.62 (broad dd, J = 5 and 1.5 Hz : 1H); 10.51 (unresolved peak : 1H); 13.15 (unresolved peak : 1H).

EI mass spectrum : m/z=326 [M+],

EXAMPLE 5

N-[6,7-difluoro-5-(4-hydroxymethyl-3-pyridinyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide :

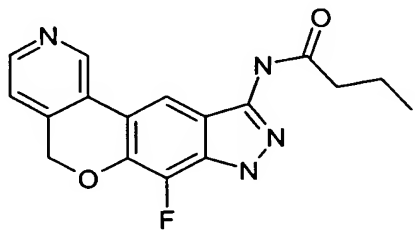


0.42 g of 3-bromo-4-hydroxymethylpyridine prepared according to S.S. Bhagwat, Bioorganic & Medicinal Chemistry Letters, 2, 1619-22, (1992), 20 cm^3 of water, 540 mg of sodium carbonate and 270 mg of tetrakistriphenylphosphine palladium are added to 0.9 g of N-[6,7-difluoro-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1-[[2-(trimethylsilyl)ethoxy]méthyl]-1H-indazol-3-yl]butanamide described above, in 100 cm^3 of dioxane. The medium is then brought to reflux for 5 hours and subsequently allowed to return to ambient temperature, and 100 cm^3 of ethyl acetate are added. The organic phase is washed twice with 100 cm^3 of distilled water and then with 75 cm^3 of a saturated aqueous sodium chloride solution, then dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 45°C) so as to give 2.0 g of yellow oil. The residue is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 3.5 cm), elution being carried out with a cyclohexane/ethyl acetate (30/70 by volume) mixture. The fractions containing the expected product are combined and evaporated under reduced pressure (2 kPa; 50°C). 0.53 mg of N-[6,7-difluoro-5-(4-hydroxymethyl-3-pyridinyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide is obtained in the form of an oil which crystallizes.

^1H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm) : - 0.06 (s : 9H); 0.86 (t, J = 8 Hz : 2H); 0.92 (t, J = 7 Hz : 3H); 1.63 (mt : 2H); 2.40 (broad t, J = 7.5 Hz : 2H); 3.61 (t, J = 8 Hz : 2H); 4.40 (d, J = 5.5 Hz : 2H); 5.47 (t, J = 5.5 Hz : 1H); 5.70 (s : 2H); from 7.45 to 7.70 (1 proton masked by the impurity P□3O); 7.70 (broad d, J = 6 Hz : 1H); 8.44 (s : 1H); 8.67 (d, J = 5.5 Hz : 1H); 10.67 (unresolved peak : 1H).

ES+ mass spectrum : m/z=477 [MH+]

N-[7-fluoro-5,8-dihydro-6-oxa-2,8,9-triazacyclopenta[b]phenanthren-10-yl)-butyramide



6.7 cm^3 of tetrabutylammonium fluoride in 1M solution in tetrahydrofuran are added to 0.53 mg of N-[6,7-difluoro-5-(4-hydroxymethyl-3-pyridinyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-indazol-3-yl]butanamide described above, in 30 cm^3 of tetrahydrofuran, and the medium is then refluxed for 18 hours and subsequently allowed to return to ambient temperature in order to add 100 cm^3 of ethyl acetate. The organic phase is washed with 75 cm^3 of a saturated aqueous sodium hydrogen carbonate solution and then with 75 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 45°C) so as to give a crude. The residue is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 2.5 cm), elution being carried out with a cyclohexane/ethyl acetate (50/50 by volume) mixture. The fractions containing the expected product are combined and concentrated to dryness under reduced pressure (2 kPa; 50°C). The residue is taken up with 10 cm^3 of diisopropyl ether, filtered through sintered glass and then washed successively with 2 times 5 cm^3 of diisopropyl ether, with 2 times 2 cm^3 of ethyl acetate and, finally, with 10 cm^3 of diisopropyl ether. After drying (90 Pa; 50°C), 40 mg of N-[7-fluoro-5,8-dihydro-6-oxa-2,8,9-triazacyclopenta[b]phenanthren-10-yl)butyramide are obtained in the form of pale yellow crystals which melt at more than 260°C.

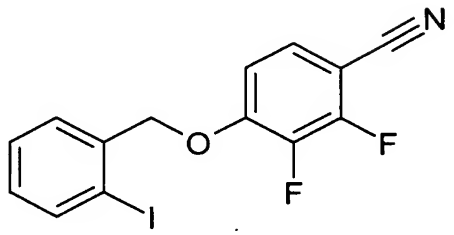
^1H NMr spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 0.99 (t, J = 7 Hz : 3H); 1.71 (mt : 2H); 2.44 (t, J = 7.5 Hz : 2H); 5.28 (s : 2H); 7.39 (broad d, J = 5.5 Hz : 1H);

8.24 (broad s : 1H); 8.53 (d, J = 5.5 Hz : 1H); 9.03 (s : 1H); 10.44 (unresolved peak : 1H); 13.16 (unresolved peak : 1H).

EI mass spectrum : m/z=326 [M+],

EXAMPLE 6

2,3-Difluoro-4-(2-iodobenzyloxy)benzonitrile

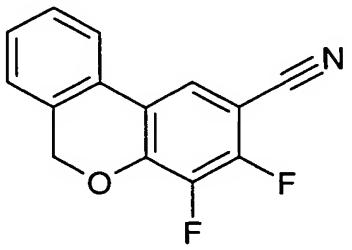


8.8 g of 1-bromomethyl-2-iodobenzene dissolved in 10 cm^3 of dimethylformamide and then 8.8 g of cesium carbonate are added to 2.0 g of 2,3-difluoro-4-hydroxybenzonitrile in 35 cm^3 of dimethylformamide, and the mixture is stirred at 4°C for 4 hours and then the reaction medium is allowed to return to ambient temperature. The reaction medium is filtered, concentrated to dryness under reduced pressure (2 kPa; 45°C) and taken up with 120 cm^3 of ethyl acetate and 30 cm^3 of water. The organic phase is washed with 30 cm^3 of water and then twice with 30 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 45°C). The residue is taken up with 20 cm^3 of diisopropyl ether, filtered through sintered glass, and then washed with 2 times 5 cm^3 of diisopropyl ether. After drying (90 Pa; 50°C), 3.0 g of 2,3-difluoro-4-(2-iodobenzyloxy)benzonitrile are obtained in the form of a sand-colored solid which melts at 104°C-106°C.

^1H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm) :5.30 (s, 2H); 7.20 (dt, J = 1.5 and 7.5 Hz, 1H); 7.40 (ddd, J = 2.0 – 7.5 and 9.0 Hz, 1H); 7.49 (dt, J = 1.0 and 7.5 Hz, 1H); 7.60 (dd, J = 1.5 and 7.5 Hz, 1H); 7.82 (ddd, J = 2.0 – 7.5 and 9.0 Hz, 1H); 7.97 (dd, J = 1.0 and 7.5 Hz, 1H).

EI-MS mass spectrum : 371(+)=(M)(+); 217(+)=base peak; 90(+)=217-I

3,4-Difluoro-6H-benzo[c]chromene-2-carbonitrile.

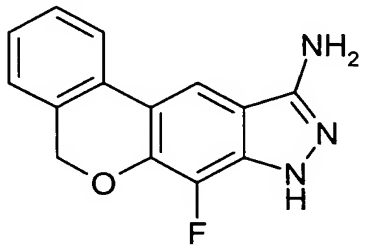


2.63 g of cesium carbonate, 30 mg of palladium acetate and 41 mg of tri-ortho-tolylphosphine in suspension in 5 cm^3 of dimethylacetamide are added successively to 1.0 g of 2,3-difluoro-4-(2-iodobenzyloxy)benzonitrile described above, in 20 cm^3 of dimethylacetamide, and the reaction medium is then heated at 85°C for 18 hours. Since the reaction is incomplete, the heating is continued at 120°C for 2 hours. After cooling, 100 cm^3 of ethyl acetate and 50 cm^3 of water are added to the reaction medium; the organic phase is separated by settling out, the aqueous phase is washed with 100 cm^3 of ethyl acetate. The organic phases are combined, washed successively with 50 cm^3 of water and 50 cm^3 of a saturated sodium chloride solution, and then dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2 kPa; 45°C) so as to give 0.73 g of crude in the form of brown oil. The residue is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 3.5 cm), elution being carried out with a cyclohexane/ethyl acetate gradient (90/10 to 80/20 by volume) mixture. The fractions containing the expected product are combined and concentrated to dryness under reduced pressure (2 kPa; 50°C), so as to give 0.11 g of 3,4-difluoro-6H-benzo[c]chromene-2-carbonitrile in the form of an 80% pure brown solid that is used as it is for the subsequent trial.

^1H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 5.44 (s, 2H); from 7.32 to 7.53 (m, 3H); 8.00 (m, 1H); 8.42 (dd, J = 2.5 and 6.5 Hz, 1H) .

EI mass spectrum : 324(+)=M(+);

7-Fluoro-5,8-dihydro-6-oxa-8,9-diazacyclopenta[b]phenanthren-10-ylamine.



0.5 cm^3 of hydrazine hydrate is added to 0.11 g of 3,4-difluoro-6H-benzo[c]chromene-2-carbonitrile described above, in 10 cm^3 of ethanol, and the mixture is refluxed for 18 hours. The reaction medium is concentrated to dryness under reduced pressure (2 kPa; 45°C). The residue is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (mean particle size 40-60 µm; diameter 2.5 cm), elution being carried out with a methylene chloride/methanol (98/2 by volume) mixture. The fractions containing the expected product are combined and concentrated to dryness under reduced pressure (2 kPa; 50°C), so as to give 0.33 g of 7-fluoro-5,8-dihydro-6-oxa-8,9-diazacyclopenta[b]phenanthren-10-ylamine in the form of a pale yellow solid which melts at 215°C-217°C

^1H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 5.19 (s, 2H); 5.55 (broad s, 2H); from 7.29 to 7.50 (m, 3H); 7.78 (broad d, J = 8.0 Hz, 1H); 8.10 (s, 1H); 11.8 (broad s, 1H) .

EI mass spectrum : 243(+)=M(+); 242(+) base peak

The pharmaceutical compositions according to the invention consist of a compound of formula (I) or a salt of such a compound, in pure form or in the form of a composition in which it is combined with any other pharmaceutically compatible product, which may be inert or physiologically active. The medicinal products according to the invention may be used orally, parenterally, rectally or topically.

Solid compositions for oral administration which may be used include tablets, pills, powders (gelatin capsules or cachets) or granules. In these compositions, the active principle according to the invention is mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under a stream of argon. These compositions may also comprise substances other than diluents, for example one or more lubricants such as magnesium stearate or talc, a colorant, a coating (for sugar-coated tablets) or varnish.

Liquid compositions for oral administration that may be used include pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs containing inert diluents such as water, ethanol, glycerol, plant oils or liquid paraffin. These compositions may comprise substances other than diluents, for example wetting agents, sweeteners, thickeners, flavorings or stabilizers.

The sterile compositions for parenteral administration may preferably be aqueous or nonaqueous solutions, suspensions or emulsions. Solvents or vehicles that may be used include water, propylene glycol, polyethylene glycol, plant oils, in particular olive oil, injectable organic esters, for example ethyl oleate, or other suitable organic solvents. These compositions may also contain adjuvants, in particular wetting agents, isotonicity agents, emulsifiers, dispersants and stabilizers. Sterilization may be carried out in several ways, for example by aseptic filtration, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions that may be dissolved at the time of use in sterile water or any other injectable sterile medium.

The compositions for rectal administration are suppositories or rectal capsules which contain, besides the active product, excipients such as cocoa butter, semisynthetic glycerides or polyethylene glycols.

The compositions for topical administration may, for example, be creams, lotions, eyewashes, mouthwashes, nasal drops or aerosols.

A subject of the invention is the tetracyclic aminoindazole compounds of formula (I), and the use thereof, and the pharmaceutically acceptable salts thereof, for the preparation of pharmaceutical compositions intended for preventing and treating diseases that may result from an abnormal activity of kinases, such as, for example, those involved in neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, frontoparietal dementia, corticobasal degeneration, Pick's disease, strokes, cranial and spinal traumas and peripheral neuropathies, obesity, metabolic diseases, type II diabetes, essential hypertension, atherosclerotic cardiovascular diseases, polycystic ovary syndrome, syndrome X, immunodeficiency, cerebral ischemia and cancer.

Examples of abnormal kinase activity that may be mentioned include that of PI3K, AkT, GSK3beta, CDK's, etc.

In human therapy, the compounds according to the invention are particularly useful for treating and/or preventing neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, frontoparietal dementia, corticobasal degeneration, Pick's disease, strokes, cranial and spinal traumas and peripheral neuropathies, obesity, metabolic diseases, type II diabetes, essential hypertension, atherosclerotic cardiovascular diseases, polycystic ovary syndrome, syndrome X, immunodeficiency, cerebral ischemia and cancer.

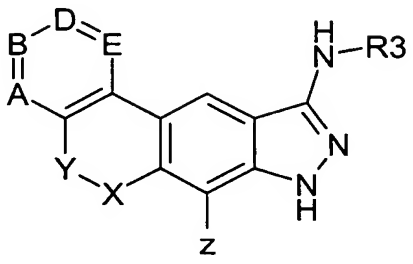
The doses depend on the desired effect, on the duration of the treatment and on the route of administration used; they are generally between 5 mg and 1000 mg per day orally for an adult, with unit doses ranging from 1 mg to 250 mg of active substance.

In general, the physician will determine the appropriate dosage depending on the age, on the weight and on all the other personal factors of the individual to be treated.

The present invention also relates to the method for preventing and treating diseases in which phosphorylation of the Tau protein is involved, by administration of a compound of formula (I) and the pharmaceutically acceptable salts thereof.

WHAT IS CLAIMED IS :

1. A compound of formula (I)



(I)

R3 represents a hydrogen or a group –C(O)-R4;

A, B, D and E represent, independently of one another, a CH or an N, in the knowledge that there are at most two nitrogens;

X represents a radical O, S, NR, CH_2, $(CH_2)_2$ or $(CH_2)_3$;

Y represents a radical CH_2, $(CH_2)_2$, CO, CS, (C=NH), O, S, NR, $C=CH_2$ or C-CHRa;

Z is a hydrogen or a halogen;

R4 is a $(C_1$-$C_6)$alkyl, aryl, aryl$(C_1$-$C_6)$alkyl, heteroaryl or heteroaryl$(C_1$-$C_6)$alkyl radical, an aryl or heteroaryl radical fused to a $(C_1$-$C_{10})$cycloalkyl radical, or a heterocyclic, cycloalkyl, adamantyl, polycycloalkyl, alkenyl or alkynyl radical; these radicals being optionally substituted with one or more substituents chosen from halogen, CN, NO_2, NH_2, OH, OR8, COOH, C(O)OR8, -O-C(O)R8, NR8R9, NHC(O)R8, C(O)NR8R9, SR8, S(O)R8, SO_2R8, $NHSO_2$R8, SO_2NR8R9, C(S)NR8R9, NHC(S)R8, -O-SO_2R8, -SO_2-O-R8, aryl, heteroaryl, formyl, trifluoromethyl, trifluoromethylsulfanyl and trifluoromethoxy;

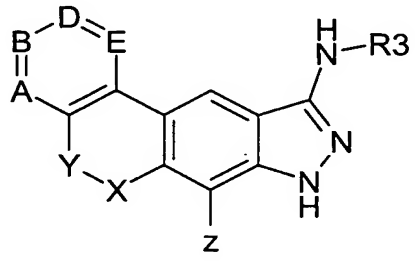
Ra is a radical OH or OR;

R is a hydrogen or a $(C_1$-$C_6)$alkyl;

R8 and R9 are, independently of one another, a hydrogen, or (C_1-C_6)alkyl, aryl, alkenyl, alkynyl or heteroaryl, themselves optionally being substituted with one or more substituents chosen from halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, CN, NO_2, NH_2, OH, COOH, COOalkyl, $CONH_2$, formyl, trifluoromethyl and trifluoromethoxy;

the racemic mixtures, enantiomers and diastereoisomers thereof and the mixtures thereof, the tautomers thereof and the pharmaceutically acceptable salts thereof.

2. A compound of formula (I)



(I)

R3 represents hydrogen or a group –C(O)-R4;

A and B independently represent a CH;

D and E represent, independently of one another, a CH or an N;

X represents a radical O or NR;

Y represents a radical CH_2, CO or $C{=}CH_2$;

Z is a halogen;

R4 is a (C_1-C_6)alkyl radical;

R is a hydrogen;

the racemic mixtures, enantiomers and diastereoisomers thereof and the mixtures thereof, the tautomers thereof and the pharmaceutically acceptable salts thereof.

3. A compound as claimed in claim 1 or 2, which is chosen from:

N-[7-fluoro-5-methylene-5,8-dihydro-6-oxa-8,9-diaza-cyclopenta[b]phenanthren-10-yl)-butyramide

N-[7-fluoro-5,8-dihydro-6-oxa-8,9-diaza-cyclopenta[b]phenanthren-10-yl)-butyramide

N-[7-fluoro-5-oxo-5,8-dihydro-6H-6,8,9-triazacyclopenta[b]phenanthren-10-yl)butyramide

N-[7-fluoro-5,8-dihydro-6-oxa-1,8,9-triazacyclopenta[b]phenanthren-10-yl)butyramide

N-[7-fluoro-5,8-dihydro-6-oxa-2,8,9-triazacyclopenta[b]phenanthren-10-yl)butyramide

7-Fluoro-5,8-dihydro-6-oxa-8,9-diazacyclopenta[b]-phenanthren-10-ylamine

the racemic mixtures, enantiomers and diastereoisomers thereof and the mixtures thereof, the tautomers thereof and the pharmaceutically acceptable salts thereof.

4. The compound as claimed in any one of claims 1 to 3, used for preparing a medicinal product.

5. A pharmaceutical composition, which comprises, in a pharmaceutically acceptable medium, the compound defined according to any one of claims 1 to 3.

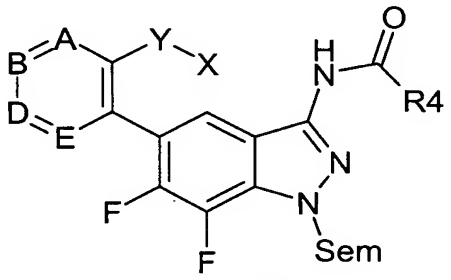
6. The medicinal product as claimed in claim 4, which contains at least one compound defined according to any one of claims 1 to 3, for its therapeutic application in the treatment of diseases in which phosphorylation of the Tau protein is observed.

7. The medicinal product as claimed in claim 4, which contains at least one compound defined according to any one of claims 1 to 3, for its therapeutic

application in the treatment of neurodegenerative diseases, strokes, cranial and spinal traumas and peripheral neuropathies, obesity, metabolic diseases, type II diabetes, essential hypertension, atherosclerotic cardiovascular diseases, polycystic ovary syndrome, syndrome X, immunodeficiency, cerebral ischemia and cancer.

8. The medicinal product as claimed in claim 7, wherein the neurodegenerative disease is either Alzheimer's disease, Parkinson's disease, frontoparietal dementia, corticobasal degeneration or Pick's disease.

9. A process for preparing the compounds of formula (I) as defined in claims 1 and 2, wherein an intermediate of formula **B** represented below is cyclized and deprotected in the presence of 6 to 10 equivalents of tetrabutylammonium fluoride at the reflux, for 2 to 10 hours, or of tetrahydrofuran.



(B)

FRAV2004/0020

FRANCE

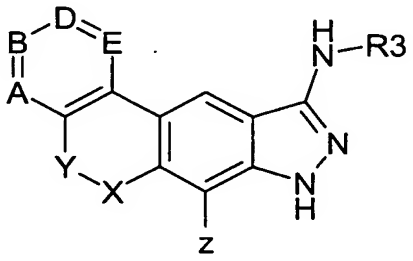
PATENT

TETRACYCLIC AMINOINDAZOLE DERIVATIVES, PREPARATION PROCESS AND INTERMEDIATES OF THIS PROCESS AS MEDICINAL PRODUCTS, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM.

AVENTIS PHARMA SA.

ABSTRACT

The present invention relates to the novel derivatives of formula (I)



in which R3 represents a hydrogen or a group –C(O)-R4; A, B, D and E represent, independently of one another, a CH or an N, in the knowledge that there are at most two nitrogens; X represents a radical O, S, NR, CH_2, $(CH_2)_2$ or $(CH_2)_3$; Y represents a radical CH_2, $(CH_2)_2$, CO, CS, (C=NH), O, S, NR, $C=CH_2$ or C-CHRa; Z is a hydrogen or a halogen; to the isomers thereof, the mixtures thereof, the racemic mixtures, enantiomers, diastereoisomers and tautomers thereof, and also the pharmaceutically acceptable salts thereof.